Remarks

Reconsideration of this Application is respectfully requested.

Claims 30, 31, 36, 44-54, 61-63, 67 and 74-76 are pending in the application, with 30, 36, 46, and 67 being the independent claims. Claims 30, 36, 61, 67 and 74 are sought to be amended. The amendments to the claims are intended to comply with the Examiner's decision to uphold the Restriction Requirement of July 8, 2005 and are not made for reasons relating to patentability. Support for these amendments may be found, *inter alia*, at page 11, ¶ [0040], and page 19, ¶ [0082] - page 20, ¶ [0087]. The specification has also been amended to include the status of the U.S. priority application, as requested by the Examiner. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Objection under 37 CFR § 1.75(d)(1) and MPEP § 608.01(o)

The Examiner has objected to the specification as allegedly not providing a proper antecedent basis for claim 30. (Office Action of March 21, 2006 (hereinafter "OA"), page 3). Specifically, the Examiner has asserted that the phrase "a purified molecule" does not have proper written support in the specification. (OA, page 3). Applicants respectfully traverse this rejection.

The specification defines and exemplifies the term "a purified molecule," and therefore provides adequate written descriptive support for the term as recited in claim

30. Section 1.75(d)(1) of Title 37, which is cited by the Examiner, states that "the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description." Accordingly, Applicants refer the Examiner to paragraph [0040] of the specification. (page 11). In that paragraph, Applicants define the term "a purified molecule" as a molecule that is "free of other antigenic molecules." (Specification, page 11, ¶ [0040]). Applicants then go on to provide examples of purified molecules, including "cytokines, particularly TNF-α and interferon-γ or other pharmaceutical drugs and the like." (Specification, page 11, ¶ [0040]). Furthermore, Example 6 of the application demonstrates that the Applicants have been able to successfully obtain a pharmaceutical composition of the present invention using antibodies generated against at least two separate purified molecules: TNF-α and interferon-γ. (Specification, page 22, ¶ [0095] - page 23, ¶ [0096]). Applicants therefore submit that the specification provides proper antecedent basis under 37 CFR § 1.75(d)(1), for the term "a purified molecule" as recited in claim 30. Reconsideration and withdrawal of the present objection is respectfully requested.

II. Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 30, 31, 36, 44, 45, 55-57, 67, 68, 71 and 74-76 under 35 U.S.C. § 112, first paragraph, for lack of enablement. (OA, page 3). More specifically, citing *In* re Wands, the Examiner has asserted that "it would take undue trials and errors" to make and/or use a pharmaceutical composition comprising an $F(ab')_2$ antibody fragment that binds and neutralizes the venom of a scorpion, as recited in the presently-pending claims, in view of: (1) the quantity of experimentation necessary, (2)

the limited working examples, (3) the unpredictability of the art, (4) the lack of sufficient guidance in the specification and (5) the breadth of the claims. (OA, page 5, 858 F.2d 731, 737 (Fed. Cir. 1988)). Applicants respectfully traverse this rejection and address each of the cited *Wands* factors below.

A. Breadth of the Claims

The Examiner states that based on the scope of the claims, "[t]he specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation." (OA, page 3). Applicants respectfully traverse.

"As concerns the breadth of a claim relevant to enablement, the only relevant concern should be whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims." MPEP § 2164.08 (citing *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003); *In re Moore*, 439 F.2d 1232, 1236 (C.C.P.A. 1971). *See also Plant Genetic Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1339 (Fed. Cir. 2003). Here, the presently-pending claims are directed to $F(ab')_2$ antibody fragments that are capable of binding and neutralizing a purified antigenic molecule or mixture of antigenic molecules found in the venom of a scorpion. Contemplation of the entire specification demonstrates that the scope of claimed subject matter is commensurate with the description of the presently-claimed invention. The specification not only describes how to obtain a pharmaceutical composition of $F(ab')_2$ antibody fragments, but it also provides examples of how to test the binding and neutralizing capabilities of the $F(ab')_2$ antibody fragments. *See* page 3, ¶ [0006], page 11, ¶ [0040] and page 23, ¶ [0097] - page 25, ¶ [0101]. Accordingly,

Applicants assert that specification as-filed provides an enabling disclosure consistent with the full scope of the presently-pending claims.

B. Guidance in the Specification

The Examiner states that "[t]he specification as filed does not provide a definition of 'neutralizing a purified antigenic molecule' in addition to [sic] insufficient guidance and direction to the nature, parameter and endpoints of 'neutralizing' the antigenic molecule." (OA, page 4). Applicants respectfully traverse.

According to Federal Circuit precedent, as discussed in the MPEP, "[a] patent need not teach, and preferably omits, what is well known in the art." § 2164.01 (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463 (Fed. Cir. 1984)). "All that is necessary is that one skilled in the art be able to practice the claimed invention given the level of knowledge and skill in the art." MPEP § 2164.08.

A person of ordinary skill in the art of immunology and/or pharmacology at the time of filing would have been capable of ascertaining the meaning of "neutralizing a purified antigenic molecule" based on intrinsic evidence provided by the specification itself, as well as available extrinsic evidence, such as a dictionary or textbook definition of the term "neutralize." For example, paragraph [0004] of the specification discusses how antibodies have been used to treat "auto-immune diseases like rheumatoid arthritis, immune-dependent diabetes mellitus, AIDS, hemophilic anaemias, rheumatic fever, multiple sclerosis, thyroiditis and psoriasis, among others." (page 2). Specifically, "[i]n

these cases, anti-cytokine antibodies are applied . . . to the patient . . . in order to remove the cytokines generated by the organism itself in response to the ailment. If such cytokines are not removed, they will cause extremely troublesome symptoms." (Specification, page 2, ¶ [0004]). A person of ordinary skill in the art would have understood that in these examples, "neutralizing" meant to apply the therapeutic $F(ab')_2$ antibody fragment composition which would bind to the target antigen and prevent or halt the immune reaction and the resulting troublesome symptoms. This definition is consistent with that provided by *Dorland's Illustrated Medical Dictionary* (Anderson, D.M., *et al.*, eds., W.B. Saunders Company, Philadelphia, p. 1135 (1994)), which defines "neutralize" as "to render neutral." Accordingly, the Applicants assert that the specification provides sufficient guidance to enable the practice of the claimed invention by a person of ordinary skill in the art at the time of filing.

C. Existence of Working Examples

The Examiner has asserted that "[t]he specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation" because there is a "lack of sufficient working examples." (OA, page 3). More specifically, the Examiner states that what "is at issue [is] whether or not the claimed invention would function as pharmaceutical composition." (OA, page 3). Applicants respectfully traverse.

The specification as-filed provides working examples that correlate with the presently-pending claims, therefore a person of ordinary skill in the art would have been able to carry out the present invention without undue experimentation. *See* MPEP §

2164.02, citing *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). Applicants have demonstrated, using both *in vitro* testing methods (Example 8) and animal testing methods (Example 7), that the $F(ab')_2$ antibody fragments of the present invention are capable of neutralizing venom. (Specification, page 23, ¶ [0097] - page 25, ¶ [0102]). Although Examples 7 and 8 are directed to $F(ab')_2$ antibody fragments that neutralize snake venom, the specification explicitly states that the antibody fragments of the present invention have been successfully generated against the venoms of a variety of poisonous animals, such as snakes, spiders and scorpions. (Specification, page 11, ¶ [0040]). These examples and descriptions demonstrate to one of ordinary skill in the art that $F(ab')_2$ antibody fragments can be made against, and subsequently used to neutralize antigenic molecules such as those found in the venom of a scorpion.

Furthermore, the proper standard for compliance with enablement is not *absolute predictability,* but *objective enablement*. *See* MPEP § 2164.05 ("The evidence provided by the applicant need not be conclusive but merely convincing to one of skill in the art.") (emphasis in original). Applicants do not need to demonstrate the clinical efficacy of the claimed composition in order to overcome the outstanding enablement rejection. There is no requirement for clinical data to prove that an application is in compliance with 35 U.S.C. § 112, first paragraph. In fact, description of *in vitro* and/or animal testing has been held to enable claims to *in vivo* therapeutic compositions and methods of their use. To this end, the Federal Circuit has stated that:

> In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo

> test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *see also In re Brana*, 51 F.3d 1560, 1567-68 (Fed. Cir. 1995) (holding that animal testing results are sufficient to establish whether one skilled in the art would believe that a pharmaceutical compound has an asserted clinical utility for the purposes of compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph).

In the specification as-filed, Applicants have provided compelling data in the Examples that should outweigh any speculative allegations of unpredictability asserted by the Examiner. Absent the Examiner providing specific evidence to the contrary, there is no reason to doubt Applicants' assertion that the claimed $F(ab')_2$ antibody fragments are fully enabled as a pharmaceutical composition that is able to bind and neutralize antigenic molecules found in scorpion venom, as recited in the presently-pending claims. *See In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971) ("[I]t is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.") (emphasis in original); *see also In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Therefore, Applicants assert that a person of ordinary skill in the art at the time of filing could have practiced the present invention without undue experimentation, in light of the working examples provided in the specification.

D. Predictability in the Art

The Examiner has raised two issues relating to the predictability in the art of the present invention with regard to the enablement rejection. First, the Examiner argues that "the lack of predictability in the art at the time the invention was made" brings into question "whether or not the claimed invention would function as a pharmaceutical composition." (OA, page 3). Second, the Examiner alleges that "[g]iven the number of possibilities associated with neutralizing an antigenic molecule . . . it would take undue experimentation to practice the claimed invention." (OA, page 4). Applicants respectfully traverse.

1. Applicants have demonstrated that the claimed invention would function as a pharmaceutical composition

As discussed above, Applicants have provided sufficient experimental data to satisfy 35 U.S.C. § 112, first paragraph, and demonstrate that the claimed invention will function as a pharmaceutical composition. Applicants have demonstrated, using both *in vitro* testing methods (Example 8) and animal testing methods (Example 7), that the claimed $F(ab')_2$ fragments are capable of neutralizing venom. (Specification, page 23, ¶ [0097] - page 25, ¶ [0102]). In Example 7, mice were injected intraperitoneally with the antivenom composition in saline, which is one example of a pharmaceutically acceptable carrier. It would be a matter of routine optimization for a person of ordinary skill in the pharmaceutical arts to prepare formulations comprising the $F(ab')_2$ antibody fragments of the present invention. The Examiner has not provided specific evidence to the contrary, therefore there is no reason to doubt Applicants' assertion that the claimed $F(ab')_2$ antibody fragments are fully enabled as a pharmaceutical composition that is able to bind

to scorpion venom. *See In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971) ("[I]t is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.") (emphasis in original); *see also In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

2. The application as-filed provides an enabling description of the presently invention, regardless of whether the mechanism of binding is disclosed

As discussed above, the Examiner has asserted that multiple possibilities associated with neutralizing an antigenic molecule necessitate undue experimentation to carry out the present invention. (OA, page 4). More specifically, the Examiner has asserted that the specification does not disclose whether the antibody would bind to specific reactive sites on the molecule, citing Burton *et al.*, *Nature Immunology* 5:233-36 (2004) (hereinafter "Burton"), for the proposition that "[b]inding of a monoclonal antibody has to be specifically at the reactive sites." (OA, page 4). The Examiner has also cited Vanlandschool [sic] *et al.*, *J. General Virology* 79:1781-1791 (1998) (hereinafter "Vanlandschoot"), as providing an example of a "monoclonal antibody [that] binds to . . . influenza virus haemagglutinin (H3 subtype) [but] does not neutralize the virus." (OA, page 4). Applicants respectfully disagree and traverse this rejection.

The specification as-filed provides an enabling disclosure of the present invention, regardless of whether the mechanism of antibody binding is disclosed. The Federal Circuit has established that it is not necessary for an applicant to understand, predict, speculate upon, or demonstrate how or why a claimed invention works. *See e.g.*,

In re Spada, 911 F.2d 705, 709 (Fed. Cir. 1990) ("an inventor is not required to understand how or why [the] invention works"); *see also Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989) ("[i]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works"), *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1570 (Fed. Cir. 1983) ("[i]t is axiomatic that an inventor need not comprehend the scientific principles on which the practical effectiveness of his invention rests"). The MPEP provides further guidance, stating that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." § 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970)). Additionally, "a specification disclosure which contains a teaching of the manner and process of making and using the invention . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support." *Rasmusson v. Smithkline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005) (quoting *In re Marzocchi*, 439 F.2d 220, 223 (C.C.P.A. 1971)).

Burton and Vanlandschoot are unrelated to the subject matter of the current invention, and therefore should not be considered with regard to the enablement of the present invention. The claimed invention is directed to $F(ab')_2$ antibody fragment compositions that bind and neutralize venom. Burton and Vanlandschoot discuss *whole* antibodies that recognize human immunodeficiency virus (HIV) and influenza virus haemagglutinin (HA), respectively. Second, although the Examiner cites these

references as standing for the proposition that antibodies can bind, yet will not neutralize, the target antigen, these references expressly provide examples of antibodies that successfully bind and neutralize the target antigen. For example, although Burton discusses the problems associated with generating neutralizing antibodies to HIV, the reference also states that "[d]espite all these defense mechanisms, primary isolates of HIV-1 from different genetic subtypes can be neutralized by some broadly reactive human monoclonal antibodies (mAB) such as b12, 2G12, 2F5 and 4E10 . . . [t]he very existence of these broadly neutralizing mABs provide some hope that a vaccine inducing [neutralizing antibodies] can indeed be created. . . ." Page 2333.

Similarly, although Vanlandschoot discusses how the authors generated an antibody that can bind, but does not inhibit HA, it also described an antibody that could bind influenza HA and prevent viral infection of cells. Page 1784. These references in no way suggest that the $F(ab')_2$ antibody fragment composition of the present invention would *not* neutralize a purified antigenic molecule or mixture of antigenic molecules found in scorpion venom. As previously discussed, the Applicants have demonstrated that their invention works using both i*n vitro* (Example 8) and animal testing (Example 7) methods, which show that the claimed $F(ab')_2$ fragments are capable of binding and neutralizing a purified antigenic molecule or mixture of antigenic molecules found in scorpion venom. (Specification, page 23, ¶ [0097] - page 25, ¶ [0102]). The Examiner has not presented any reason to doubt the objective truth of these experimental results, therefore under *Marzocchi* and *Rasmusson*, the present specification "must be taken as in compliance with the enabling requirement of the first paragraph of § 112." Reconsideration and withdrawal of this rejection is respectfully requested.

E. Quantity of Experimentation Needed to Practice the Present Invention

The Examiner has asserted that based on the "amount experimentation required to enable one of skilled in the art to practice the claimed invention, "[t]he specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation." (OA, page 3). Applicants respectfully traverse.

A person of ordinary skill in the art could practice the present invention without undue experimentation, based on the guidance in the specification and the level of skill in the art. Undue experimentation does not mean "no" experimentation, only that it be reasonable. *See, e.g., In re Wands*, 858 F.2d at 737 ("The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."). As discussed above, the specification as-filed not only describes how to obtain a pharmaceutical composition of $F(ab')_2$ antibody fragments, but it also provides examples of how to test the binding and neutralizing capabilities of the $F(ab')_2$ antibody fragments. *See* page 3, ¶ [0006], page 11, ¶ [0040] and page 23, ¶ [0097] - page 25, ¶ [0101]. A person of ordinary skill in the art at the time of filing would have possessed the skills necessary to make, test and/or administer the compositions of the present invention, based on the direction and guidance provided in the specification. Thus, any experimentation required to practice the present invention would have been reasonable, not undue. Applicants respectfully request that this rejection be reconsidered and withdrawn.

In summary, claims 30, 31, 36, 44, 45, 55-57, 67, 68, 71 and 74-76 are fully enabled by the specification. Therefore, Applicants respectfully request reconsideration and withdrawal of the present rejection.

II. Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 30, 36, 44, 45, 55, 67, 68 and 76 under 35 U.S.C. § 102(b) as allegedly being anticipated by Sullivan *et al.* (U.S. Patent No. 4,849,352) (hereinafter "the '352 patent") as evidenced by Harlow and Lane (*Antibodies*, Harlow, E. and Lane, D., eds., Cold Spring Harbor Laboratory Press, pp. 298-99) (1988) (hereinafter "Harlow") and Campbell (*Monoclonal and Immunosensor Technology*, Campbell, A., ed., Elsevier Science, pp. 288-91) (1991) (hereinafter "Campbell"). (OA, page 5). Applicants respectfully traverse this rejection.

The Examiner has asserted that the '352 patent "teaches a pharmaceutical composition comprising a polyclonal $F(ab')_2$ [sic] binds to any antigen." (OA, page 5). To anticipate a claim, the reference must teach *every* element of the claim. *See* MPEP § 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicants respectfully assert that the '352 patent does not teach every element recited in the presently-pending claims, and therefore does not anticipate the present invention.

The present invention is directed to a pharmaceutical composition comprising polyclonal $F(ab')_2$ antibody fragments substantially free from *whole antibodies*. In contrast, the '352 patent describes $F(ab')_2$ fragments isolated from antigen-immobilized affinity columns that are not free from whole antibodies. The '352 patent discloses

contacting an antibody source with a pepsin-polyacrylamide matrix to produce $F(ab')_2$ and F(c) fragments that are then passed through an antigen-polyacrylamide gel. col. 5, ll. 57-68. As the inventors of the '352 patent admit, the initial antibody cleavage step is unable to fully digest the antibody source. col. 10, ll. 21-24. The resultant digestion product will therefore be a mixture of $F(ab')_2$ fragments, F(c) fragments, and uncleaved whole antibody. Due to the fact that the antigen in the antigen-polyacrylamide gel is capable of binding both $F(ab')_2$ antibody fragments and whole antibody, the product disclosed in the '352 patent will be a mixture of both $F(ab')_2$ antibody fragments and whole antibodies. col. 8, l. 6 - col. 9, l. 9. All of the claims in the present application recite a composition that is substantially free of whole antibodies. The '352 patent therefore does not teach every element of the present invention as recited in the pending claims. The present invention is therefore novel and not anticipated by the '352 patent.

Additionally, claims 36, 44, 67 and 76 are directed to $F(ab')_2$ antibody fragments that are capable of binding and neutralizing a purified antigenic molecule or a mixture of antigenic molecules found in the venom of scorpion, which are obtained by a specific process using two steps of ammonium sulfate precipitation. *See* MPEP § 2173.05(p)(I) ("A product-by-process claim, which is a product claim that defines the claimed product in terms of the process by which it is made, is proper.") (citing *In re Luck*, 476 F.2d 650, 177 (C.C.P.A. 1973); *In re Pilkington*, 411 F.2d 1345 (C.C.P.A. 1969); *In re Steppan*, 394 F.2d 1013 (C.C.P.A. 1967)). Specifically, the process steps recited in the presently-pending claims remove whole antibodies from the digested composition. The '352 patent does not disclose these specific process steps or any process steps that inherently remove whole antibodies. Since each and every element recited in the presently-pending claims

is not disclosed by the '352 patent, expressly or inherently, the '352 patent cannot anticipate the claimed invention. *See Verdegaal Bros.*, 814 F.2d at 631.

The Examiner's rejection under 35 U.S.C. §102(b) over the '352 patent includes consideration of two additional references, Harlow and Campbell, as allegedly teaching the two steps of ammonium sulfate precipitation recited in the presently-pending claims. (OA, page 5). Applicants respectfully remind the Examiner that, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a *single* prior art reference." *Verdegaal Bros.*, 814 F.2d at 631 (emphasis added). Inclusion of the Harlow and Campbell references in the Examiner's 102(b) rejection is therefore improper according to statutory and Federal Circuit precedent.

Furthermore, assuming *arguendo* that it was permissible to combine the '352 patent with Harlow and Campbell under 35 U.S.C. §102(b), a person of ordinary skill in the art would not have been motivated to do so because the '352 patent actually teaches away from pepsin digestion followed by ammonium sulfate precipitation. (OA, page 5). The '352 patent lists "examples of antivenin antibodies which are pepsin digested and then precipitated with ammonium sulphate [sic];" however, the '352 patent also explicitly states that "such enzyme digestion and ammonium precipitation procedures do not remove all foreign proteins . . . [c]onsequently, some bite victims undergoing antivenin treatment suffer extreme allergic reactions to those foreign proteins which are not removed. . . ." col. 2, l. 51 - col. 3, l. 2. The named inventors on the '352 patent go as far as to emphasize the fact that their invention does not require an ammonium sulfate

precipitation step. col. 6, ll. 53-55. ("Hence applicants have negated the need for the ammonium sulfate precipitation procedures used in producing commercial antivenins."). The '352 patent therefore discloses the production of antivenom using a procedure that does not involve an ammonium sulfate precipitation step. Consequently, a person of ordinary skill in the art would not have been motivated to combine the process of the '352 patent with an ammonium sulfate precipitation step, as allegedly disclosed in Harlow and Campbell, to arrive at the present invention.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 30, 36, 44, 45, 55, 67, 68 and 76 under 35 U.S.C. § 102(b).

III. Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 30, 31, 36, 44, 45, 55-57, 67, 68, 71 and 74-76 as allegedly being obvious over U.S. Patent No. 5,443,976 (hereinafter "the '976 patent") in view of U.S. Patent No. 4,849,352 (hereinafter the "the '352 patent") as evidenced by Harlow and Lane (*Antibodies*, Harlow, E. and Lane, D., eds., Cold Spring Harbor Laboratory Press, pp. 298-99) (1988) (hereinafter "Harlow") and Campbell (*Monoclonal and Immunosensor Technology*, Campbell, A., ed., Elsevier Science, pp. 288-91) (1991) (hereinafter "Campbell"). (OA, page 7). More specifically, the Examiner stated

> one of ordinary skill in the art would have been motivated to combine teachings of antibody to scorpion venom *Centruroids noxius* taught by the '976 patent in the teachings of the '352 patent to produce more readily utilizable antibody to scorpion venom.

Id. Applicants respectfully traverse this rejection

The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). A *prima facie* case of obviousness cannot be established unless all of the claim elements are taught or suggested by the cited references. *See In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42 (Fed. Cir. 2002); *In re Rijckaert*, 9 F.3d 1531, 1533 (Fed. Cir. 1993). In addition, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *See In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). If, however, one of the references teaches away from the combination, it is improper to combine the references. *See* MPEP § 2145(X)(D)(2). In the present case, the Examiner's burden has not been satisfied because there is no motivation to combine the cited references.

1. The '976 patent teaches away from the present invention

A person of ordinary skill in the art would not have been motivated to combine the disclosures of the '976 patent and the '352 patent to arrive at the presently claimed invention because the '976 patent teaches away from making $F(ab')_2$ antibody fragments for use as antivenom. Furthermore, even if a person of ordinary skill in the art did combine these two references, he or she would not arrive at the present invention. Therefore, Applicants respectfully submit that the Examiner has failed to make a *prima facie* case of obviousness.

The '976 patent discloses a method of making and purifying antivenoms, preferably by immunizing chickens, collecting IgY from egg yolk, and purifying the venom specific IgY using an antigen matrix. col. 12, l. 61 - col. 13, l. 27. The only discussion of $F(ab')_2$ antibody fragments in the '976 patent makes reference to the problems associated with generating $F(ab')_2$ antibody fragments for use as antivenom:

> [t]he potency of individual lots of antivenoms will vary because of two principal factors. First, because the whole antisera or immunoglobulin fractions used and the specific antibody titer per unit volume will vary from animal to animal and from day to day, the amount of venom-reactive antibodies will differ from preparation to preparation. Second, *refinement procedures such as ammonium sulfate precipitation and pepsin digestion can reduce the yield of active antibody, causing variations in the titer of active ingredient per unit volume.* These difficulties are exacerbated when antivenom is raised against a set of venoms in order to treat a range of species.

col. 6, ll. 20-32 (emphasis added). Thus, the '976 patent teaches away from making $F(ab')_2$ antibody fragments for use as antivenom, particularly against a range of species.

Since the '976 patent only mentions $F(ab')_2$ antibody fragments in passing as a less desirable method for producing a different product than was the focus of the patent, a person of ordinary skill in the art would have no reason to seek out additional references discussing $F(ab')_2$ antibody fragments. Therefore, a person of ordinary skill in the art would not have been motivated to combine the teachings of the '976 patent with the '352 patent to arrive at a pharmaceutical composition comprising polyclonal $F(ab')_2$ antibody fragments capable of binding and neutralizing a purified antigenic molecule or a mixture of antigenic molecules found in scorpion venom, as recited in the presently-

pending claims. Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness. Reconsideration and withdrawal of this rejection is requested.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider all currently outstanding objections and rejections and that they be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all currently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Laura Vogel

Laura A. Vogel
Attorney for Applicants
Registration No. 55,702

Date: 9/21/06

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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